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14. ABSTRACT

This project aims to gain a better understanding of the implications of genetic testing for breast-ovarian cancer susceptibility. The primary goal is to evaluate the impact of BRCA1/BRCA2 mutation testing on long term psychosocial (quality of life, distress, social functioning) and prevention/surveillance (mammography, CA125, transvaginal ultrasound, prophylactic mastectomy, prophylactic oophorectomy and chemoprevention) outcomes. To accomplish this we will measure outcomes within a group of women who received BRCA1/BRCA2 test results at least four years ago. We will divide our sample based upon their personal cancer history – evaluating cancer survivors with different measures compared to unaffected individuals. For both survivors and unaffected individuals we will recruit separate comparison samples of women who have never received BRCA1/BRCA2 testing.

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INTRODUCTION

Genetic testing for breast-ovarian cancer susceptibility has the potential to reduce breast and ovarian cancer mortality among high risk women. However, there has been ongoing concern regarding the quality of life implications of learning one's mutation status. To date, there have been no studies to evaluate the long-term psychosocial and behavioral impact of receiving clinical *BRCA1/BRCA2* gene test results. Several studies have examined these outcomes in the short-term. Although preliminary evidence suggests that the receipt of a positive *BRCA1/BRCA2* test result does not lead to increased short-term distress, it is clear that women who receive positive test results do report more distress than those who receive negative test results. It is not clear, however, whether this distress has long-term implications. It is possible that distress could decline over time as the individual adapts to her positive test result and ongoing risk. Alternatively, the modestly elevated distress reported in the short-term could be evidence of chronic stress. Ongoing stress has been shown to adversely impact health behaviors and health outcomes. Given the risk status of this population, it is particularly important to better understand the long-term distress levels and the role of distress in adoption of recommended breast and ovarian cancer risk reduction and early detection behavior. To date, there have been no studies to examine these issues.

One of the main potential benefits of *BRCA1/BRCA2* testing is to motivate carriers to take behavioral action to reduce their risk of breast and ovarian cancer mortality. However, we do not yet know whether carriers actually engage in such actions. Preliminary evidence suggests that a relatively small proportion of carriers obtain prophylactic surgery in the year following testing. The proportion of carriers who utilize chemopreventive agents such as tamoxifen remains unknown. The few studies to examine screening utilization in the year following disclosure found sub-optimal rates of screening among positives. In fact, rates of mammography have not been found to increase following a positive mutation test. Although mutation carriers did report higher rates of mammography, this difference was due to appropriate decreases in screening among younger noncarriers. In terms of ovarian cancer screening, rates of CA-125 and transvaginal ultrasound do increase among carriers in the year following testing. However, overall ovarian cancer screening rates remain below 30%. To date, there have been no studies to evaluate the long-term cancer prevention and screening behaviors of this population. If genetic testing is to fulfill its promise of reducing mortality among individuals from hereditary cancer families, behavioral change must follow the receipt of a positive test result. The first step to addressing this question is to evaluate the behavior of individuals in the years following testing. If individuals remain non-adherent to prevention and screening guidelines, it is particularly important to understand why and to identify early predictors of behavioral non-adherence in this vulnerable population. We will evaluate the role of distress/quality of life as a potential predictor of adverse behavioral outcomes.

The primary goal of this project is to evaluate long term psychosocial (quality of life, distress, social functioning) and prevention/surveillance (mammography, CA-125, transvaginal ultrasound, prophylactic mastectomy, prophylactic oophorectomy and chemoprevention) outcomes. To accomplish this we will measure outcomes within a group of women who received *BRCA1/BRCA2* test results at least four years ago. We will divide our sample based upon their personal cancer history – evaluating cancer survivors with different measures compared to unaffected individuals. For both survivors and unaffected individuals we will recruit separate comparison samples of women who have never received *BRCA1/BRCA2* testing.

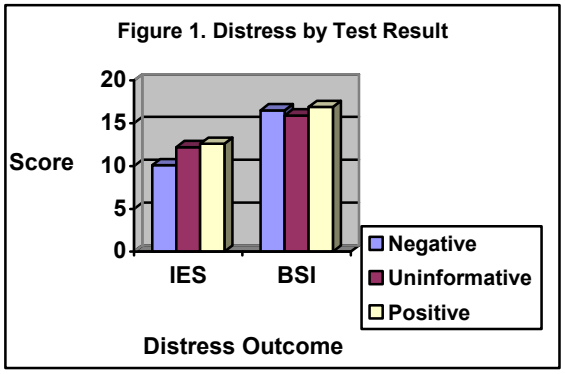
Until we better understand the long-term outcomes of BRCA1/2 testing, it is unlikely that such testing will fulfill its promise to reduce breast and ovarian cancer mortality. By evaluating the impact of

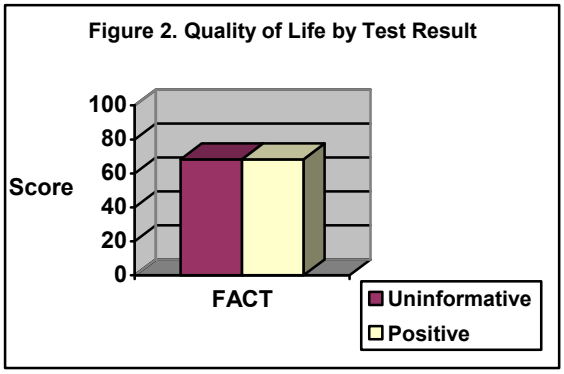
testing, appropriate intervention strategies can be developed so that individuals at-risk for distress or non-adherence could be targeted for early intervention and/or ongoing support. This research could provide information necessary to make decisions about how and where to allocate scarce counseling resources and to tailor health promotion efforts to individual needs. Genetic testing for breast-ovarian cancer susceptibility is becoming more widely available to the general population. Prior to its routine use, we should make sure that we fully understand its long-term implications.

BODY

Of the women enrolled in the study to date, 13% are under age 40, 95% are college graduates, 91% are Caucasian, 67% are married, and 35% are Ashkenazi Jewish. In terms of medical status, 78% have been previously diagnosed with breast or ovarian cancer. In terms of test results, 29% received a positive BRCA1/2 test result, 60% received uninformative test results and 11% received definitive negative test results.

We are currently preparing a manuscript describing psychosocial and quality of life outcomes. The results stratified by test result group are displayed in Figures 1 and 2. As seen in these figures, there were no differences in distress or quality of life by test result (p>.10)





In a manuscript currently under revision, we examined familial communication of genetic test results. Data for this manuscript were based on 274 women who had completed an interview by the time of data analysis for this paper. Demographic characteristics of the women who participated are as follows: *M* (*SD*) age = 54.1 (9.6) years, 91.1% Caucasian, 96.4% college-educated, and 70.2% lived in households with a family income $\geq$\$75*k*. The *M* (*SD*) calendar time that had elapsed since testing averaged 5.3 (1.2) years.

Table 1. Family Structure and Closeness Ratings

Relative Category	N	%	M (SD) closeness
Parents	158	57.7	
Mothers	126	46.0	3.8 (0.5)
Fathers	116	42.3	3.6 (0.8)
Siblings	238	86.9	
Sisters	173	63.1	3.7 (0.7)
Brothers	139	50.7	3.4 (0.9)
Spouses	214	78.1	3.9 (0.5)
Children	185	68.9	
$\leq$ 18	55	29.7	3.8 (0.3)
< 18	130	70.3	3.9 (0.5)

Data regarding women's family structure are presented in Table 1. As shown, more than one-half of women were able to report on family communication to parents, over three-quarters reported on communication to siblings and spouses, and slightly more than two-thirds reported on communication to children.

When family communication was analyzed via disclosure (Yes/No) to relatives, rates of communication to adult relatives was consistently high: 94.4% reported disclosing their *BRCA1/2* test results to their mothers, 87.1% to their fathers, 96.5% to their sisters, 84.2% to their brothers, 98.1% to their spouses, and 95.3% to their children over the age of 18; disclosure was less common to children under the age of 18 (53.6%).

To examine the potential impact of test results (i.e., carriers vs. uninformatives) on disclosure patterns to relatives, the association between these variables was tested via Chi-square statistics. There were no significant differences in rates of disclosure between carriers and uninformatives to all relatives

except for brothers; carriers were more likely to disclose their test results to their brothers than were uninformatives, X^2 (1) = 8.14, p = .004.

Table 2. Association of closeness with disclosure

Relatives	r_{pb}	$sr_y(1.2)$
Mothers	.25*	.25*
Fathers	.28*	.30*
Sisters	.16*	.16*
Brothers	.40*	.39*
Spouses	.20*	.21*
Children ≥ 18	.25*	.25*
Children < 18	-.09	-.10

Note. r_{pb} denotes point-biserial correlation between closeness and disclosure; $s_{ry(1.2)}$ denotes semi-partial correlation between closeness and disclosure, controlling for test results.

Finally, the potential association between kinship and disclosure was examined via point-biserial correlations, with and without the potential impact of test results partialled out. These results, shown in Table 2, consistently indicate that women who reported stronger kinship ties and closer relationships with their adult relatives during the time they underwent *BRCA1/2* testing were more likely to inform those relatives of their results. The strength of these associations remained largely unchanged when genetic test results were accounted for. For children under the age of 18 years, closeness was not associated with disclosure.

We have submitted a second manuscript which evaluates risk management outcomes within this sample. This manuscript is based on an abstract presented at the annual meeting of the American Society of Preventive Oncology[1]. For this manuscript we assessed the long-term rates and predictors of Risk Reducing Mastectomy (RRM) and Risk Reducing Oophorectomy (RRO). Participants were women with ≥10% probability of carrying a BRCA1/2 mutation who received genetic testing 4-8 years earlier. For RRM analyses, women (n=454) had no history of breast cancer or had unilateral breast cancer. For RRO analyses, women (N=486) had no history of ovarian cancer. Women completed assessments before and 4-8 years (M=5.3 yrs) after testing.

Among women without bilateral mastectomy before testing (13% had prior bilateral mastectomy), 38% with positive test results ultimately had RRM. Among women without oophorectomy before testing (19% had prior oophorectomy), 64% of positives ultimately had RRO. Most women opting for RRM did so within one year of testing (72%), while only 39% of those with RRO had it within a year.

RRM was strongly predicted by positive test result (χ^2 (df=2; N=393) = 69.3, p<.001). Among mutation carriers, those most likely to opt for RRM had a stronger family history (OR=3.5, 95% CI = 1.42-8.73) and were more anxious prior to genetic testing (OR=1.55, 95% CI = 1.04, 2.32). RRO was also strongly predicted by test result (χ^2 (df=2; N=390) = 105.2, p<.001). Among carriers, RRO was predicted only by age. Specifically, carriers age 40 or above were more than 8-fold more likely to opt for RRO (OR=8.5, 95% CI=3.2-22.0). At follow-up, women with RRM or RRO did not differ from women without surgery on quality of life or distress. Risk reducing surgery is being appropriately utilized by women at the highest risk of HBOC and does not appear to adversely impact long-term psychological outcomes.

In another abstract we evaluated the long term outcomes among *BRCA1/BRCA2* uninformatives[2]. In terms of surveillance for breast cancer, most women had a mammogram (84%) and a clinical breast exam (94%) within the past year. Of the women with no prior history of ovarian cancer, 12% (n=26) reported RRO prior to receipt of test results, 10.1% (n=22) reported RRO after receipt of test results, and 77.9% (n=169) reported never having RRO. RRO was obtained an average of 2.75 years after receipt of test results (range 0.1 to 5.0 yrs). The RRO groups (never, prior, and after testing) did not differ on long-term quality of life outcomes (p<.41); however, the groups significantly differed on global distress (F=4.96, p<.01), with women who had RRO after testing reporting more distress than women who had RRO before testing.

Regardless of RRO status, greater long term cancer-specific distress among uninformatives was predicted by greater levels of baseline cancer-specific distress prior to receipt of test result (β=.30, $p<.001$), higher current perceived risk of cancer (β= .23, $p<.01$), and ovarian cancer family history, specifically a greater number of relatives affected by ovarian cancer (β= .22, $p<.01$). A trend was found where RRO timing and status (never, prior to testing, after testing) was associated with current cancer-specific distress (β= -.15, p=.07), with BPO after receipt of uninformative results marginally related to higher current levels of cancer-specific distress.

KEY RESEARCH ACCOMPLISHMENTS

Our research accomplishments to date include:

- Enrolling and completing interviews with over 600 participants
- Demonstrating extremely high rates of family communication among women who receive positive BRCA1/BRCA2 gene test results
- Documenting that the vast majority of women who receive a positive *BRCA1/BRCA2* gene test result opt for risk reducing surgery
- Demonstrating that over 20% of carriers who do not opt for risk reducing surgery use chemoprevention
- Documenting no long-term adverse psychosocial outcomes associated with receipt of a positive *BRCA1/BRCA2* test result.

REPORTABLE OUTCOMES

Manuscripts

1. Tercyak, K.P, Graves, K.D., Peshkin, B.N. and Schwartz, M.D. (2008). Long-term follow-up of women's decisions to share *BRCA1/2* test results with first-degree relatives. Under Editorial Review.

2. Schwartz, M.D., Graves, K.D., Peshkin, B.N., Taylor, K.L., Gell, C., Zawastowski, G., Poggi, E., (2009). Long-term management decisions following *BRCA1/2* gene testing. Under Editorial Review.

3. Schwartz, M.D., Graves, K.D., Peshkin, B.N., Taylor, K.L., Gell, C., Zawastowski, G., Poggi, E., (2009). Long-term impact of *BRCA1/2* test results on psychosocial outcomes. In Preparation.

Abstracts

1. Graves KD, Gell CE, Hecker SL, Peshkin BN, Taylor KL, Schwartz MD. (2007). Long-Term Prophylactic Surgery Outcomes following BRCA1/2 Genetic Testing. Presented at the annual meeting of the American Society of Preventive Oncology.

2. Vegella P, Graves K, Kelleher S, Kelly S, Zawistowski G, Porter A, DeMarco T, Peshkin B, Schwartz M. (2008). Long Term Outcomes of Affected Women who Received Uninformative BRCA1/2 Test Results. Presented at the annual AACR Frontiers in Cancer Prevention Meeting.

Presentations

1. Schwartz, M.D. Impact of uncertainty on genetic testing outcomes. To be presented at the International Hereditary Breast Ovarian Cancer Symposium, Montreal, October 2009.

CONCLUSIONS

This project seeks to gain a better understanding of the long-term psychosocial and behavioral implications of undergoing genetic counseling and testing for breast-ovarian cancer susceptibility. Since the start of the study, we have prepared all of our data collection and data management tools, hired our study staff, begun regular meetings, and compiled lists of participants to be contacted for participation. However, due to delays on the part of the Department of Defense Human Subjects review, we have been unable to commence study accrual and interviewing. After receiving final DOD approval, we initiated accrual and have been completing interviews at the expected pace.

REFERENCES

1. Graves KD, Gell CE, Hecker SL, Peshkin BN, Taylor KL, Schwartz MD. (2007). Long-Term Prophylactic Surgery Outcomes following BRCA1/2 Genetic Testing. Presented at the annual meeting of the American Society of Preventive Oncology.

2. Vegella P, Graves K, Kelleher S, Kelly S, Zawistowski G, Porter A, DeMarco T, Peshkin B, Schwartz M. (2008). Long Term Outcomes of Affected Women who Received Uninformative BRCA1/2 Test Results. Presented at the annual AACR Frontiers in Cancer Prevention Meeting.

APPENDIX A: Current Salaried Study Personnel

The no cost extension on this project has ended. Thus, we currently have no salaries personnel on this project. However, we continue to accrue participants to this project using institutional funds.

Appendix B

Abstract 1

Long-Term Prophylactic Surgery Outcomes following BRCA1/2 Genetic Testing.

Graves KD, Gell CE, Hecker SL, Peshkin BN, Taylor KL, Schwartz MD.

Purpose: Women with a BRCA1/2 mutation may choose to reduce their breast and ovarian cancer risk through prophylactic mastectomy (PM) and/or prophylactic oophorectomy (PO). We assessed the long-term rates and predictors of PM and PO. Methods: Participants were women with ≥10% probability of carrying a BRCA1/2 mutation who received genetic testing 4-8 years earlier. For PM analyses, women (n=307) had no history of breast cancer or had unilateral breast cancer. For PO analyses, women (N=342) had no history of ovarian cancer. Women completed assessments before and 4-8 years (M=5.3 yrs) after testing. Results: Among women without PM before testing (14% had prior PM), 35% with positive test results ultimately had PM. Among women without oophorectomy before testing (29% had prior PO), 46% of positives ultimately had PO. Most women opting for PM did so within one year of testing (72%), while only 39% of those with PO had it within a year. PM was predicted by positive test result (OR=6.6, 95%CI=2.8-15.7) and being affected with unilateral breast cancer (OR=4.4, 95%CI=1.5-12.6). PO was predicted by age ≥40 (OR=6.8, 95%CI=2.0-23.1), positive test result (OR=18.1, 95%CI=7.8-41.9) and having PM (OR=7.8, 95%CI=2.8-21.6). At follow-up, women with prophylactic surgery did not differ from women without surgery on quality of life or distress. Summary: Prophylactic surgery is being appropriately utilized by women at the highest risk of HBOC and does not appear to adversely impact long-term psychological outcomes.

Appendix C

Abstract 2

Long-Term Outcomes of Affected Women who Received Uninformative *BRCA1/2* Results

Patti Vegella, Kristi Graves, Scott Kelly, Grace Zawistowski, Allison Porter, Beth Peshkin, Tiffani DeMarco, & Marc Schwartz.

Little is known about long-term behavioral and psychological outcomes following receipt of an uninformative *BRCA1/2* genetic test result. The purpose of this study was to examine the behavioral, medical, and psychosocial outcomes. Specifically, we evaluated long-term bilateral prophylactic salpingo-oophorectomy (BPO) rates, current quality of life (QOL) outcomes, and predictors of distress for women affected with breast cancer who received an uninformative result.

Method:
Participants were women with a 10% or greater likelihood of carrying a *BRCA* mutation who had received genetic counseling and genetic test results 4-8 years prior. All women in the present sample (N = 230) received uninformative *BRCA1/2* test results and were affected with breast cancer. Women completed assessments measuring demographics, global distress (BSI), cancer-specific distress (IES), risk perceptions, surgery and surveillance behaviors, and quality of life (FACT) before and 4-8 years (M=5.8 yrs) after genetic testing.

Analyses/Results:
In terms of surveillance for breast cancer, most women had a mammogram (84%) and a clinical breast exam (94%) within the past year. When evaluating BPO surgery outcomes, we eliminated women who had been diagnosed with ovarian cancer (n = 13). Of the women with uninformative results and no prior history of ovarian cancer, 12% (n=26) reported BPO prior to receipt of test results, 10.1% (n=22) reported BPO after receipt of test results, and 77.9% (n=169) reported never having BPO. BPO was obtained an average of 2.75 years after receipt of test results (range 0.1 to 5.0 yrs). The BPO groups (never, prior to testing, after testing) did not differ on long-term QOL outcomes ($p<.41$); however, the groups significantly differed on global distress ($F=4.96$, $p<.01$), with women who had BPO after testing reporting more distress than women who had BPO before testing. Regardless of BPO status, greater long term cancer-specific distress among uninformatives was predicted by greater levels of baseline cancer-specific distress prior to receipt of test result ($\beta=.30$, $p<.001$), higher current perceived risk of cancer ($\beta= .23$, $p<.01$), and ovarian cancer family history, specifically a greater number of relatives affected by ovarian cancer ($\beta= .22$, $p<.01$). A trend was found where BPO timing and status (never, prior to testing, after testing) was associated with current cancer-specific distress ($\beta= -.15$, $p=.07$). Specifically, having BPO after receipt of uninformative results was marginally related to higher current levels of cancer-specific distress.

Conclusions:
Previous studies have found that the uninformative group is diverse in their psychosocial outcomes and this study is among the first to report long-term behavioral and psychosocial outcomes among women who receive uninformative *BRCA1/2* genetic test results. Women who opt for BPO after notification of an uninformative result appear to have higher current global distress than women who never had BPO or those who had the surgery prior to receipt of test results, with a similar trend for current cancer-specific distress. Our findings suggest that women who receive uninformative test results, mainly those with a strong family history of ovarian cancer, high cancer-specific distress prior

to genetic testing, and those who opt for BPO following result notification, may benefit from routine long-term follow up from genetic counselors.